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Noise and air pollution and the incidence of dementia: a cohort study in London

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Abstract

Objectives

To investigate whether the incidence of dementia is related to residential levels of air and noise pollution in London.

Design

Retrospective cohort study using primary care data.

Setting

75 Greater London practices.

Participants

130,978 adults aged 50-79 years registered with their general practices on 1/1/2005, with no history of dementia or care home residence.

Primary and Secondary Outcome Measures

A first recorded diagnosis of dementia, and where specified, sub-groups of Alzheimer's and vascular dementia during 2005-11. Average annual concentrations during 2004 for nitrogen dioxide (NO_2), particulate matter with a median aerodynamic diameter ≤2.5µm ($PM_{2.5}$) and ozone (O_3) were estimated at 20m x 20m resolution from dispersion models. Traffic intensity, distance from major road and night-time A-weighted noise levels (L_{night}) were estimated at postcode level. All exposure measures were linked anonymously to clinical data via residential postcode. Hazard ratios (HRs) from Cox models were adjusted for age, sex, smoking, BMI, area deprivation and co-morbidity.

Results

1,527 subjects (1.2%) received an incident diagnosis of dementia (35% mentioning Alzheimer's disease, 29% vascular dementia). There was a positive exposure response relationship between dementia and all measures of air pollution except O_3, which was not readily explained by further adjustment. Adults living in areas with the highest fifth of NO_2 concentration (>41.5 µg/m^3) versus the lowest fifth (<31.9 µg/m^3) were at higher risk of dementia (HR=1.58, 95% CI 1.24-2.01). Increases in dementia risk were also observed with $PM_{2.5}$, $PM_{2.5}$ specifically from primary traffic sources only, and L_{night}, but only NO_2 and $PM_{2.5}$ remained statistically significant in multi-pollutant models. Associations were more consistent for Alzheimer's disease than vascular dementia.

Conclusions

We have found evidence of a positive association between residential levels of air pollution across London and being diagnosed with dementia, which is unexplained by known confounding factors.

Word Count = 291 words

Strengths and Limitations of this study (5 Max)

- Annuals concentrations of air and noise pollution exposure was modelled at a fine resolution including roadside estimates of traffic pollution
- Anonymous linkage of pollution data to electronic health records of over 100,000 older adults registered with 75 general practices in Greater London during 2005-2011
- Incident dementia diagnoses were identified including Alzheimer's disease and vascular dementia
- Robustness of results was tested for by adjusting for area deprivation and other co-morbidities
- Accuracy and completeness of primary care diagnoses of dementia and sub-diagnoses is a known issue

Background

Dementia, encompassing both vascular dementia and Alzheimer's disease, is now reported as the leading cause of death in England and Wales accounting for 12% of all registered deaths.[1] While temporal changes in recording may have influenced how underlying cause is now determined, more important are increases in longevity among the population at older ages, caused by declining trends in deaths from cardiovascular and cerebrovascular disease.[2] In terms of years of life lost, the Global Burden of Disease in 2013 ranked all dementia as the fifth leading cause,[2] noting their increasing importance as a cause of death despite little change in age-standardised rates. Therefore, primary prevention of all dementia is a major global public health concern for the coming decades.[3] For Alzheimer's disease for example, while it has been estimated that small delays in its onset and progression could significantly reduce its estimated future burden,[4] research has primarily focussed on lifestyle factors where a large systematic review estimated that about a third of Alzheimer's disease may be attributable to potentially modifiable risk factors such as smoking and physical inactivity.[5]

More recently research has also extended to the role of environmental risk factors and dementia, where a large systematic review identified moderate evidence for an association with 8 different factors including air pollution.[6] While air pollution is a well-established risk factor for cardiovascular and respiratory disease,[7] its role in relation to dementia is less well considered and understood.[8] A recent systematic review of the epidemiologic evidence linking air pollution to dementia related outcomes, identified 18 studies, with most reporting adverse associations.[9] However, there was significant variation in the size and quality of the studies involved, re-iterating the noted lack of robust longitudinal or population based studies[6,8]. Subsequently, a large population-based study in Ontario, Canada reported that living close to major roads was associated with a higher incidence of dementia,[10] with a further analysis revealing corresponding associations with modelled levels of nitrogen dioxide (NO_2) and mass of fine particulate matter with a median aerodynamic diameter ≤2.5μm ($PM_{2.5}$).[11] These findings not only raise questions around the mechanisms for the early development of neuroinflammation and neurodegeneration,[12] but require further exploration and replication in other large population cohorts with different exposure models, including traffic noise which has been linked to cognitive decline in adults.[13]

In this paper, we use modelled estimates at a fine spatial scale for modelled estimates of air and noise pollution to investigate relationships with the incidence of dementia across Greater London.

Methods

Data Source

The Clinical Practice Research Datalink (CPRD) is a large, validated primary care database that has been collecting anonymous patient data from participating UK general practices since 1987.[14] Approximately three-quarters of contributing CPRD practices have consented to their data being linked to external sources. These include the Index of Multiple Deprivation (IMD), a composite small-area (approximately 1500 people) measure used in England for allocation of resources,[15] and

Office for National Statistics (ONS) death registration data, which allows underlying cause of death to be identified. For this study, we selected 75 (linked) practices that lay within the study area bounded geographically by the orbital M25 motorway around Greater London that were continually recording data between 2004-2011.[16]

Estimates of Air and Noise Pollution Exposure

The following measures of exposure were linked to CPRD: (i) annual air pollution concentrations, (ii) traffic intensity or distance measures, (iii) road traffic noise levels.

Modelled annual concentrations for air pollutants were estimated using the KCLurban dispersion modelling system at a resolution of 20m x 20m.[17] It incorporates hourly meteorological measurements, empirically derived concentrations of NO-NO_2-O_3 and derived PM (particulate matter), using information on source emissions from the London Atmospheric Emissions Inventory.[18] For this analysis, we focused on annual concentrations in 2004 for NO_2 (nitrogen dioxide), $PM_{2.5}$ (fine particulate matter with a median aerodynamic diameter ≤2.5μm) and O_3 (ozone). Additionally, we present an estimate for primary $PM_{2.5}$ attributable to road traffic sources estimated from the sum of contributions from the following emissions sources: tyre, brake, exhaust, surface wear and resuspension.[17] Air pollution concentration estimates for each of the 190,115 London postcodes address centroid, which typically average about 15 households, were based on interpolation from the closest 20x20m point of the dispersion model.[18] These were then linked by a “trusted third party” to CPRD, ensuring we had no direct access to the postcodes, preserving patient anonymity.

Traffic proximity measures were developed relating to ‘heavy’ vehicle density, which was defined as: light goods vehicles, heavy goods vehicles (rigid and articulated trucks/lorries), buses and coaches. We included a distance measure (in metres) from the postcode centroid to the nearest road classified in the top quartile of heavy vehicle intensity. Traffic intensity was estimated as total vehicle km driven (heavy vehicles only) in each year for all major roads that fell within a 50m and 50-100m radius of the postcode address centroid. We used an arbitrary cut-off >100,000km driven to define ‘high volume’ in the analyses.

Road traffic noise levels were estimated using the TRAffic Noise EXposure (TRANEX) model[19]. This uses information on road traffic flows and speeds, road geography, land cover, and building heights to estimate average sound pressure level (LA_{eq}) in decibels (dB) over different time periods. Evaluations of TRANEX in two other English cities have shown high correlation (r≥0.85) between modelled and measured one-hour LA_{eq}[19]. In our analysis, we focused on average annual L_{night} recorded overnight between 23:00-07:00, as this period represents when most of our study subjects would be at their residence. Alternative analyses using daytime noise (L_{Aeq16}) produced identical results due to the extremely high correlation with night noise (r=0.999).[20] For the linkage of the noise model to CPRD, the geometric centroids of the address locations in each postcode were directly used.

Cohort Definition

139,718 adults were identified aged 50-79 years who were alive and actively registered as of 1/1/2005 for ≥1 year continuously with their practice. From this group, 131,869 (94%) were successfully linked to our pollution exposures. Non-linkage was mainly due to a few practices being near the study area boundary, so many of their patients' individual postcodes were not eligible.

We searched the primary care records for the date of first dementia diagnosis, using the Read codes for dementia within the Quality and Outcomes Framework (QOF).[21] Although most Read codes are non-specific, we identified sub-groups that classified the dementia as Alzheimer's disease or vascular dementia. Using the death records, we also used ICD-10 codes to identify any patients with dementia as a cause of death who had not been coded as such on their GP record. Following previous methods[16], we also collated information on ethnicity, smoking, BMI and alcohol consumption, primarily using the last measurement before baseline, retaining a missing category where the information was not available. In addition, we identified selected co-morbidities (Ischaemic Heart Disease (IHD), stroke, heart failure, diabetes) that were independently predictive of dementia.

Patients (n=391) with an existing diagnosis for dementia by 1/1/2005 were excluded. Additionally, we sought to exclude patients (n=423) where there was evidence on their medical record that they were living in a residential or care home as of 1/1/2005. We did this through a combination of Read codes, or where 4 or more patients aged 65-99 were recorded living at the same address. We also excluded a small number of patients (n=77) where no IMD could be assigned. This resulted in 130,978 eligible patients for our analyses.

Statistical Analyses

We used Cox proportional hazards models to investigate associations between all exposure measures estimated in the year before baseline (2004) and subsequent dementia incidence. To account for the clustering by practice (homogeneity between patients from the same practice), we fitted models with a shared frailty (at practice level), which are the survival data equivalent to random effects.[22] We adjusted cumulatively for: (1) age, sex, ethnicity, smoking, alcohol consumption and BMI, (2) IMD Decile (based on national ranking across England), (3) Co-morbidities, (4) Other pollutants (air pollution for noise and vice versa). Additionally for (1), we fitted a non-frailty model stratified on practice, to provide an estimate of a within-practice effect. We also carried out a sensitivity analyses using alternative methods (practice as fixed effect, fitting practice mean level) to obtain a within-practice effect. For all pollutants, we fitted a continuous measure based on an inter-quartile range to enable comparison between estimates, and quintile categories to describe the shape of the association. All analyses were carried out in Stata version 13 (StataCorp LP, College Station, TX, USA).

Results

A total of 1,527 patients (1.2%) received a first diagnosis of dementia during follow-up (Table 1). Among those patients diagnosed, 530 (34.7%) had a mention of Alzheimer's disease, 436 (28.6%) mentioned vascular dementia, while 589 (38.6%) received a non-specific read code. A total of 28 patients (1.8%) received diagnoses for both Alzheimer's disease and vascular dementia, while 589 patients (38.6%) only received non-specific diagnoses. Mean follow-up time was 5.8 years.

Table 1 – Characteristics of eligible subjects

Baseline Variable	Grouping	All Eligible Patients*		First Diagnosis of Dementia 2005-2011†							
				Any		Alzheimer's		Vascular		Non-specific	
		n	%	n	%	n	%	n	%	n	%
	All	130,978	100	1,527	100	530	100	436	100	589	100
Gender	Men	65,130	49.7	674	44.1	206	38.9	205	47.0	278	47.2
	Women	65,848	50.3	853	55.9	324	61.1	231	53.0	311	52.8
Age	50-59	59,587	45.5	68	4.5	24	4.5	11	2.5	33	5.6
	60-69	41,013	31.3	284	18.7	104	19.6	72	16.5	111	18.9
	70-79	30,378	23.2	1,175	76.9	402	75.9	353	81.0	445	75.6
Ethnicity	White	86,896	66.3	1,269	83.1	446	84.2	365	83.7	485	82.3
	Asian	7,309	5.6	72	4.7	19	3.6	30	6.9	23	3.9
	Black	4,287	3.3	70	4.6	19	3.6	23	5.3	28	4.8
	Unknown	32,486	24.8	116	7.6	46	8.7	18	4.1	53	9.0
Smoking	Never	63,478	48.5	767	50.3	291	54.9	203	46.6	282	47.9
	Ex	33,063	25.2	509	33.3	174	32.8	159	36.5	190	32.3
	Current	25,733	19.7	217	14.2	56	10.6	62	14.2	104	17.7
	Missing	8,704	6.7	34	2.2	9	1.7	12	2.8	13	2.2
Co-Morbidity	IHD	9,928	7.6	244	16.0	56	10.6	98	22.5	95	16.1
	Stroke	3,647	2.8	143	9.4	22	4.2	73	16.7	53	9.0
	Diabetes	10,160	7.8	210	13.7	52	9.8	82	18.8	81	13.8
	Heart Failure	1,704	1.3	54	3.5	8	1.5	22	5.1	24	4.1
Index of Multiple Deprivation‡	1 (Least)	26,149	20.0	298	19.5	96	18.1	88	20.2	124	21.1
	2	31,452	24.0	375	24.6	125	23.6	104	23.9	151	25.6
	3	26,093	19.9	284	18.6	119	22.5	76	17.4	95	16.1
	4	30,817	23.5	353	23.1	123	23.2	104	23.9	130	22.1
	5 (Most)	16,467	12.6	217	14.2	67	12.6	64	14.7	89	15.1

* - Registered on 1/1/2005, for at least one year, no history of dementia with no care home markers on record on that date (see methods)

† - N=28 patients appear in both Alzheimer's and vascular dementia category

‡ - These groups correspond to fifths of IMD ranking across England, thus Greater London is under represented in the most deprived fifth.

Table 2 summarises modelled air and noise pollutants by traffic distance and intensity. All pollutants declined with increasing distance from major roads, except O_3 which was higher with further distance, because of the strong negative correlation (r=-0.9 or greater) with both NO_2 and $PM_{2.5}$. While patients residing in postcodes closest to major roads (0-50m) had much higher night noise levels than those furthest away (60.4 vs. 50.9dB), the difference in modelled air pollution concentrations, especially $PM_{2.5}$, was much less. While NO_2 and $PM_{2.5}$ were highly correlated (r=0.98), correlations between them and night noise, while still strongly positive, were less in magnitude (r=0.3-0.4).

Table 2 – Summary of air (NO_2, $PM_{2.5}$, $PM_{2.5}$ Traffic, O_3) and noise (L_{night}) pollutants by traffic volume and major road distance

Traffic exposure	Level	N		NO_2	$PM_{2.5}$	$PM_{2.5}$ (Traffic)	O_3	L_{night}
All		130,978	Mean ±SD	37.1 ±5.7	15.7 ±0.8	1.4 ±0.5	38.0 ±3.9	52.1 ±4.6
			Median	36.4	15.6	1.3	38.2	49.9
			IQR‡	32.9-40.4	15.2-16.1	1.1-1.7	35.5-41.0	49.4-52.1
Vehicle km Driven*	None within 100m	74,913	Mean ±SD	35.8 ±4.6	15.5 ±0.6	1.3 ±0.3	38.8 ±3.4	49.9 ±1.2
	Low within 50-100m	15,995	Mean ±SD	36.5 ±5.0	15.6 ±0.7	1.3 ±0.4	38.3 ±3.7	50.3 ±1.4
	Low within 50m	23,243	Mean ±SD	38.5 ±5.9	15.9 ±0.8	1.6 ±0.5	37.3 ±4.1	57.2 ±4.8
	High within 50-100m	10,400	Mean ±SD	39.6 ±5.9	16.1 ±0.8	1.7 ±0.5	36.3 ±4.1	52.2 ±3.1
	High within 50m	6,427	Mean ±SD	45.6 ±7.3	17.0 ±1.0	2.6 ±0.8	33.2 ±4.3	62.6 ±5.9
Distance(m) to major road†	>250m	59,825	Mean ±SD	35.2 ±4.7	15.4 ±0.7	1.2 ±0.3	39.3 ±3.5	50.9 ±3.3
	100-250m	43,386	Mean ±SD	37.7 ±5.1	15.8 ±0.7	1.4 ±0.4	37.5 ±3.6	51.2 ±3.2
	50-100m	14,708	Mean ±SD	39.4 ±6.0	16.0 ±0.8	1.7 ±0.5	36.5 ±4.1	52.5 ±3.8
	0-50m	12,609	Mean ±SD	41.9 ±7.2	16.5 ±1.0	2.1 ±0.8	35.4 ±4.5	60.4 ±5.7

Note: Pearson correlations between modelled pollutants were: NO_2 and $PM_{2.5}$ =0.98, NO_2 and $PM_{2.5}$ (Traffic) = 0.94, NO_2 and O_3 =-0.99, NO_2 and L_{night} =0.33, $PM_{2.5}$ and $PM_{2.5}$ (Traffic) = 0.97, $PM_{2.5}$ and O_3 =-0.96, $PM_{2.5}$ and L_{night} =0.39, $PM_{2.5}$ (Traffic) and O_3 =-0.90, $PM_{2.5}$ (Traffic) and L_{night} =0.51, O_3 and L_{night} =-0.27.

* >100,000km driven annually by heavy vehicles (see methods) was defined as High Volume, <100,000km defined as Low Volume.

† - Major road defined as top quartile of heavy vehicle intensity

‡ - Inter-quartile range

Table 3 summarises a series of adjusted hazard ratios for an incident diagnosis of dementia associated with comparable inter-quartile changes in different pollutant exposures. The strongest positive associations were seen for NO_2 where a +7.5 μg/m^3 change produced a HR=1.22 (95% CI 1.10-1.35), adjusting for IMD and other confounders (HR3 in Table 3). Corresponding associations were smaller with other measures ($PM_{2.5}$ HR=1.09, $PM_{2.5}$ Traffic HR=1.12, L_{night} HR=1.04, Distance from road HR=1.05) or negative (O_3 HR=0.81). Fitting a model stratified by practice to estimate a within-practice estimate, widened confidence intervals, but did not suggest the association was being driven by between-practice differences in air or noise pollution. Other approaches to adjusting for the practice clustering still suggested a similar within-practice estimate (Table S1).

To investigate the shape of the association, Figure 1 plots the adjusted hazard ratio (HR3 in Table 3) by air and noise pollution fifths, and road distance and traffic intensity 50m categories. For NO_2 and $PM_{2.5}$ the increase in dementia risk rises with each quintile. Patients residing in the top quintile of NO_2 (>41.5 μg/m^3) had a marked increase in risk (HR=1.58, 95% CI 1.24-2.01) compared to those in the bottom quintile (<31.9 μg/m^3). For other measures (noise, distance, intensity) generally only the highest category showed an increased risk for dementia, while for O_3 the risk declined with increasing exposure.

The associations between dementia and an interquartile change (+7.5 μg/m^3) in NO_2 are explored further in Figure 2, which plots adjusted hazard ratios (HR2 in Table 3) from Cox models stratified on a series of risk factors. Generally, there was little evidence of any effect modification across these factors, with all categories producing a HR>1. Associations between NO_2 and dementia were still observed when restricted to patients registered for their practice continually for more than 10 years (HR=1.20, 95%CI 1.07-1.35), or to patients without IHD, stroke, dementia or heart failure at baseline (HR=1.27, 95%CI 1.14-1.41).

Table 3 – Adjusted hazard ratios for incident Dementia during 2005-2011 by traffic related exposures

Exposure	IQR Change	HR1[a] (95% CI)	HR2[b] (95% CI)	HR3[c] (95% CI)	HR4[d] (95% CI)	HR5[e] (95% CI)
NO_2	+7.47 μg/m^3	1.22 (1.10-1.35)	1.23 (1.11-1.36)	1.22 (1.10-1.35)	1.19 (1.06-1.33)	1.21 (1.02-1.44)
$PM_{2.5}$	+0.95 μg/m^3	1.10 (1.04-1.15)	1.10 (1.04-1.15)	1.09 (1.04-1.15)	1.08 (1.02-1.15)	1.07 (1.00-1.15)
$PM_{2.5}$ (Traffic)	+0.58 μg/m^3	1.13 (1.05-1.22)	1.13 (1.04-1.22)	1.12 (1.04-1.21)	1.09 (0.99-1.20)	1.08 (0.98-1.20)
O_3	+5.56 μg/m^3	0.80 (0.72-0.90)	0.80 (0.71-0.90)	0.81 (0.72-0.91)	0.83 (0.73-0.94)	0.78 (0.61-1.00)
L_{night}	+ 2.68 dB	1.04 (1.01-1.07)	1.04 (1.01-1.07)	1.04 (1.01-1.07)	1.02 (0.99-1.05)	1.03 (1.00-1.06)
Distance to major road	- 310 m	1.05 (0.99-1.12)	1.06 (0.99-1.12)	1.05 (0.99-1.12)	1.02 (0.95-1.09)	1.03 (0.96-1.10)

[a] HR1: Cox model with practice fitted as shared-frailty. Adjusted for age, gender, ethnicity, smoking, alcohol consumption & BMI.
[b] HR2: As HR1, plus additional adjustment for IMD.
[c] HR3: As HR2, plus additional adjustment for co-morbidity (IHD, Stroke, Diabetes, Heart Failure).
[d] HR4: As HR3, plus additional adjustment for L_{night} (NO_2 and $PM_{2.5}$ estimates) or NO_2 (L_{night} and Distance estimates).
[e] HR5: As HR1, but stratified by practice rather than shared-frailty.

We repeated the analysis, sub-classifying dementia diagnoses as Alzheimer's disease or vascular dementia where possible (Table 4). Associations were more consistent for Alzheimer's disease. Patients in the top quintile of NO_2 were at twice the risk of for receiving an Alzheimer's diagnosis than patients in bottom quintile (HR=2.04, 95% CI 1.39-2.97). For vascular dementia, there was less evidence of a consistent effects with air or noise pollution, though a formal statistical comparison of estimates lacked power to test this (p=0.22 for NO_2 trend difference)

Table 4 – Hazard ratios for incident Alzheimer's disease and vascular dementia during 2005-2011 by air and noise pollutants

		Alzheimer's Disease	Vascular Dementia	Non-specific
Exposure	**Category / IQR Change**	**HR2**[a] (95% CI)	**HR2**[a] (95% CI)	**HR2**[a] (95% CI)
NO_2	0-31.9	1 (Reference)	1 (Reference)	1 (Reference)
	>31.9-35.2	1.16 (0.83-1.62)	0.98 (0.67-1.44)	1.12 (0.85-1.47)
	>35.2-37.5	1.34 (0.93-1.92)	0.94 (0.60-1.45)	0.99 (0.73-1.33)
	>37.5-41.5	1.62 (1.13-2.33)	1.19 (0.75-1.87)	1.00 (0.73-1.36)
	>41.5	2.04 (1.39-2.97)	1.12 (0.68-1.84)	1.54 (1.14-2.09)
	+7.5 $\mu g/m^3$	1.40 (1.19-1.65)	1.19 (0.96-1.47)	1.13 (0.98-1.29)
$PM_{2.5}$	0-15.1	1 (Reference)	1 (Reference)	1 (Reference)
	>15.1-15.4	1.25 (0.90-1.74)	0.92 (0.64-1.32)	1.07 (0.81-1.41)
	>15.4-15.7	1.42 (1.00-2.03)	0.75 (0.49-1.14)	1.10 (0.82-1.46)
	>15.7-16.3	1.73 (1.21-2.46)	1.05 (0.68-1.62)	1.03 (0.76-1.39)
	>16.3	1.89 (1.30-2.76)	0.88 (0.54-1.43)	1.43 (1.05-1.94)
	+0.9 $\mu g/m^3$	1.18 (1.09-1.27)	1.06 (0.96-1.18)	1.06 (0.99-1.14)
$PM_{2.5}$ Traffic	0-1.04	1 (Reference)	1 (Reference)	1 (Reference)
	>1.04-1.22	1.10 (0.79-1.53)	1.19 (0.84-1.68)	1.25 (0.69-1.92)
	>1.22-1.42	1.24 (0.88-1.74)	1.01 (0.68-1.48)	1.05 (0.78-1.40)
	>1.42-1.75	1.56 (1.11-2.19)	0.94 (0.62-1.43)	1.05 (0.77-1.41)
	>1.75	1.86 (1.30-2.66)	1.02 (0.66-1.60)	1.48 (1.10-2.00)
	+0.58 $\mu g/m^3$	1.25 (1.11-1.41)	1.07 (0.92-1.25)	1.08 (0.96-1.20)
0_3	0-34.7	1 (Reference)	1 (Reference)	1 (Reference)
	>34.7-37.3	0.88 (0.66-1.18)	0.94 (0.63-1.40)	0.70 (0.53-0.93)
	>37.3-39.1	0.61 (0.44-0.86)	0.82 (0.53-1.27)	0.72 (0.53-0.96)
	>39.1-41.8	0.60 (0.42-0.85)	0.81 (0.51-1.28)	0.72 (0.54-0.97)
	>41.8	0.51 (0.35-0.75)	0.83 (0.50-1.39)	0.69 (0.51-0.94)
	+5.6 $\mu g/m^3$	0.68 (0.56-0.82)	0.85 (0.66-1.09)	0.89 (0.76-1.03)
L_{night}	0-49.4	1 (Reference)	1 (Reference)	1 (Reference)
	>49.4-49.6	0.97 (0.73-1.29)	1.16 (0.84-1.59)	0.96 (0.74-1.24)
	>49.6-50.3	0.93 (0.70-1.24)	1.21 (0.88-1.65)	0.92 (0.71-1.20)
	>50.3-53.8	1.04 (0.78-1.38)	1.16 (0.84-1.60)	0.89 (0.68-1.16)
	>53.8	1.19 (0.91-1.57)	1.11 (0.80-1.52)	1.18 (0.92-1.52)
	+ 2.7 dB	1.05 (1.00-1.10)	1.01 (0.97-1.07)	1.05 (1.00-1.10)

[a] HR2: Cox model with practice fitted as shared-frailty. Adjusted for age, gender, ethnicity, smoking, alcohol consumption, BMI & IMD.

Discussion

In a sample of 75 general practices across Greater London the recording of new dementia diagnoses was positively associated with measures of NO_2 and $PM_{2.5}$ assigned at residential address at beginning of the incident period. The association could not be explained by confounding, and was consistent within sub-groups. When we restricted to specific diagnoses, associations were still observed with Alzheimer's disease but not vascular dementia.

Strengths and Weaknesses

The main strengths of our study are that its size and length of follow-up allowed sufficient incident diagnoses of dementia to be accumulated for adequate power. The longitudinal medical record allowed us to exclude patients already diagnosed with dementia, and classify (albeit with limited success) type of dementia during follow-up. However there are concerns around the variability of dementia diagnoses in UK primary care,[23] and a recent review has concluded that dementia diagnoses on primary care databases may not be an accurate reflection of the true prevalence.[24] Under-recording is thought to be a common issue, as the diagnosis is associated with a stigma for many, and GP's may be reluctant to diagnose dementia unless highly certain[25]. A recent study across 23 London practices increased the prevalence on their QOF dementia registers by 9% by a simple coding review.[25] Under-recording in our study could be problematic if it was related to key practice characteristics such as deprivation, as dementia recording has been shown to be lower among more affluent practices.[23,26] Although we had no further access to practice specific characteristics, our findings were unchanged when the analysis was stratified by practice or IMD.

Another concern was the possibility that the geographical location of elderly care homes was associated with pollution measures. If (undiagnosed) patients already resident in care homes at the beginning of our study, were subsequently receiving a first dementia diagnosis during follow-up, this may result in a spurious association with our exposure measures. To discount this, we excluded patients estimated to be in a care home due to unusual clustering of their address flag among all older patients, or other specific markers in their electronic record that indicated care home residence at baseline. Although we cannot completely rule out misclassification as an explanation for the geographical patterns in dementia we have observed, they would have to specific to dementia, as previous analyses of this cohort using cardiovascular and respiratory incident outcomes largely failed to find associations with the modelled pollution estimates.[16]

A novel aspect of our analysis was the ability to simultaneously study the modelled effects of air and noise pollution on dementia, overcoming acknowledged limitations from other studies.[11,27] Previous validation of the pollution models used in this study had shown low roadside correlation between them, suggesting that the independent effects of traffic pollution and road noise can be investigated.[20] However, there remains uncertainty around exposure assignment at address level, where an annual estimate for a single year (2004) is used to represent long-term exposure, based on the last known address for the patient at that practice. Our pollution models were not available prior to 2004, so our analysis assumes that exposure at baseline will act as proxy for exposure many years and decades before, where the pathogenesis of Alzheimer's disease may have already begun.[28] Capturing an accurate picture of lifetime or cumulative exposure is further complicated by our cohort being based around London where the population is mobile and dynamic over time.[29] Sensitivity analyses based on patients who had been continually registered at their practice for a long time (>10years) produced similar findings. Where we did have other modelled years available during follow-up (2005-2010), these were highly correlated over time, so alternative analyses using them made no discernible difference. A further issue could be that recent exposure levels are acting as a proxy for other historical environmental factors linked to pollution, such as lead from petrol,[30] where cumulative exposure has been linked to cognitive decline in later life.[31]

Another limitation is that by being based within Greater London, our exposure estimates may be somewhat homogeneous, lacking the variability we would expect to see nationally when more rural geographical areas are included. Within London, the contribution of regional (background) $PM_{2.5}$ and O_3 to overall levels tends to dominate.[17] However, we were able to make use of a dispersion model with exceptionally fine resolution (20m x 20m), to estimate significant changes in exposure of air pollution such as NO_2, between major roads and suburban background locations.[17] Despite this, the reality was that subtle roadside changes predicted by the model were small in comparison to larger differences estimated between the areas represented by the GP practices, suggesting most modelled variation was between (practice) areas.[16] While this limited statistical power to look at within practice effects, we still estimated positive associations for both NO_2 and $PM_{2.5}$ when the models were stratified by practice.

Context

The established body of epidemiological evidence linking long term concentrations of air pollution to adverse health effects has mainly focussed on cardiovascular disease[32]. The Global Burden of Disease studies which have described the worldwide impact of air pollution, considered a wide range of outcomes (ischaemic heart disease, stroke, lung cancer, chronic obstructive pulmonary disease) but did not consider neurodegenerative outcomes.[7] Research linking air pollution exposure to neurocognitive function has gradually increased from observational findings in 2002 from dogs in Mexico City,[33] to larger studies which assessed cognitive decline,[34,35] and large population cohorts that specifically investigated the association in relation to diagnoses of dementia.[10,11,36-38]

A 2015 review on the effect of long-term exposure to outdoor air pollution (15 studies) and noise (8 studies) on cognitive and psychological functions in adults showed that both exposures were separately shown to be associated with one or several measures of global cognitive function, but no study considered both exposures simultaneously, which they highlighted as a need for further research.[27] The same authors followed with data from the Heinz Nixdorf Recall cohort study,[13] on 4,086 adults using an additively calculated global cognitive score. They concluded “air pollution and road traffic noise might act synergistically on cognitive function in adults”. Our study could consider both measures (air pollution and night noise), and while both showed independent associations with dementia, in a combined model any associations with noise were diminished and of borderline statistical significance.

The largest studies using diagnoses of dementia are by Chen et al[10,11] who used a large Canadian population based cohort of over 2 million adults aged 55-85 years to ascertain approximately

250,000 incident dementia cases during 2001-13. In their first analysis,[10] the authors found that the risk of dementia increased with nearness to a major road (adjusted HR=1.07 95%CI 1.06–1.08, for people living <50m from a major traffic road versus >300m). Associations were stronger among urban residents, especially those who lived in major cities. In a subsequent analysis,[11] they used land-use regression models to estimate associations between incident dementia and air pollution, findings significant positive associations with both $PM_{2.5}$ and NO_2, and smaller negative assciations with O_3. An interquartile-range increase in $PM_{2.5}$ (4.8μg/m^3) was associated with a HR=1.04 (95%CI 1.03–1.05), while for NO_2 (14.2ppb) it was estimated to be HR=1.10 (95%CI 1.08–1.12). By comparison, our estimated distribution of the same pollutants within Greater London was much less spread, with IQRs almost a fifth smaller. Therefore, comparative HR's for similar unit changes in our study are much greater (e.g. for a 1μg/m^3 change in $PM_{2.5}$ the HR would be 1.08 compared to 1.01 from the Canadian study, for NO_2 this would be 1.02 vs. 1.00). The authors speculate that the stronger associations observed with NO_2 may be in part be due to it better capturing fine-scale variability in traffic-related air pollution, whereas $PM_{2.5}$ and O_3 have larger regional components.[11] However the resolution of their air pollution models was coarser (1km^2 resolution) than in our study (20m^2) and may not capture primary emissions from road traffic. While our models were able to estimate traffic-specific components of $PM_{2.5}$,[17] effect estimates remained higher for NO_2.

Some smaller studies have separated Alzheimer's disease from dementia. In Europe, a 15-year longitudinal study in northern Swedish city found evidence of positive associations with both with vascular dementia and Alzheimer's disease and Nitrogen Oxide (NO_x) using a land-use regression model with a spatial resolution of 50m^2. Comparison between participants in the highest quartile of residential exposure at baseline, versus those in the lowest, produced similar estimates were similar for Alzheimer's disease (HR=1.38) and vascular dementia (HR=1.47). There have been recent cohort studies from Taiwan: Jung el al[36] showed long-term exposure to O_3 and $PM_{2.5}$ was shown to increase risk of Alzheimer's, while Chang et al[38] found associations between dementia and NO_2 and carbon monoxide. A smaller case-control study by Wu et al[39] linked PM_{10} and O_3 to an increased risk of Alzheimer's and (vascular) dementia. In our study, lower O_3 was negatively associated with risk of dementia, primarily as a result of the strong negative correlation with the other modelled air pollutants.[40]

Implications

The implications of linking exposure to air pollution such as NO_2 to the development of dementia, specifically Alzheimer's disease, raises many questions.[12] The cause of these neurodegenerative diseases is still largely unknown and may be multifactorial.[8] While toxicants from air pollution have several plausible pathways to reach the brain, how and when they may influence neurodegeneration remains speculative.[8,28,41] Traffic related air pollution has been linked to poorer cognitive development in young children,[42] and continued significant exposure may produce neuroinflammation and altered brain innate immune responses in early adulthood.[43] In later life, the risk for accelerated cognitive decline may involve gene-environment interactions, such as that with Apolipoprotein E (APOE),[44] where evidence comes from findings in neurotoxicological experiments with mice.[45]

Our observation of an association of air pollution with new dementia diagnoses among older adults living in Greater London, are in contrast to an earlier analysis on this data which failed to show consistent associations between air pollution and cardiorespiratory outcomes.[16] These suggest a geographical pattern specific to dementia, and potentially Alzheimer's disease, which require further exploration nationally. In the Ontario cohort, Chen et al estimated that 6.1% of their total dementia cases were attributable to elevated air pollution exposure.[11] In our study, a theoretical shift of all patients to the bottom 20% of NO_2 exposure produces an attributable fraction of 13% (data not shown). This would be higher than many previous PAF estimates for dementia in the UK for a range of independent risk factors, such as for hypertension or obesity, with only physical activity (21.8%) producing a higher estimate.[5] While our results should be treated with caution, even a small PAF for dementia would be impactful, where environmental risk factors such as air pollution can be more easily modified at population level.[28] There would be significant public health gains even if the impact was only to delay the progression of dementia.[4]

With the future global burden of dementia likely to be substantial,[3] further epidemiological work is urgently needed to confirm and understand better, recent findings linking air pollution to dementia.[8,28] Our results suggest both regional and urban background pollutants may be as important as near-traffic pollutants. Future large-scale studies will need to rely on improved recording and linkage of dementia diagnoses across electronic systems, particularly Alzheimer's disease, where multiple sources can improve diagnostic accuracy.[24] Since exposure is lifelong, and most cases are diagnosed in later life, historical data is also ideally required to better estimate cumulative exposure over preceding decades. In conclusion, our findings add to a growing evidence base linking air pollution and neurodegeneration, and should encourage further research in this area.

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Contributors: HRA, RWA, JG, SDB, and FJK contributed to the wider study conception and design. HRA, SDB, JG, DD, and FJK contributed to exposure assessment. IMC, RWA and DGC acquired linked health data. IMC conceived the specific study design, conducted the data analyses, and drafted the initial report. HRA, RWA,

DGC and DPS all contributed to the data analysis plan. All authors contributed to interpreting the analyses and to critically revising the article and approved the final draft. IMC is the guarantor of the work.

Conflicts of Interest: None

Data Sharing: Not available

Figure 1 – Adjusted hazard ratios (HRs) for all incident dementia during 2005-2011 by air and noise pollution fifths and traffic distance and intensity categories

HRs estimated from cox model with practice fitted as shared-frailty. Adjusted for age, gender, ethnicity, smoking, alcohol consumption, BMI, IMD and co-morbidity (IHD, Stroke, Diabetes, Heart Failure, COPD).

Figure 2 – Stratified adjusted hazard ratios (HRs) for an inter-quartile increase (7.5 μg/m^3) in NO_2 and all incident dementia during 2005-2011

HRs estimated from cox model with practice fitted as shared-frailty. Adjusted for age, gender, ethnicity, smoking, alcohol consumption and BMI.

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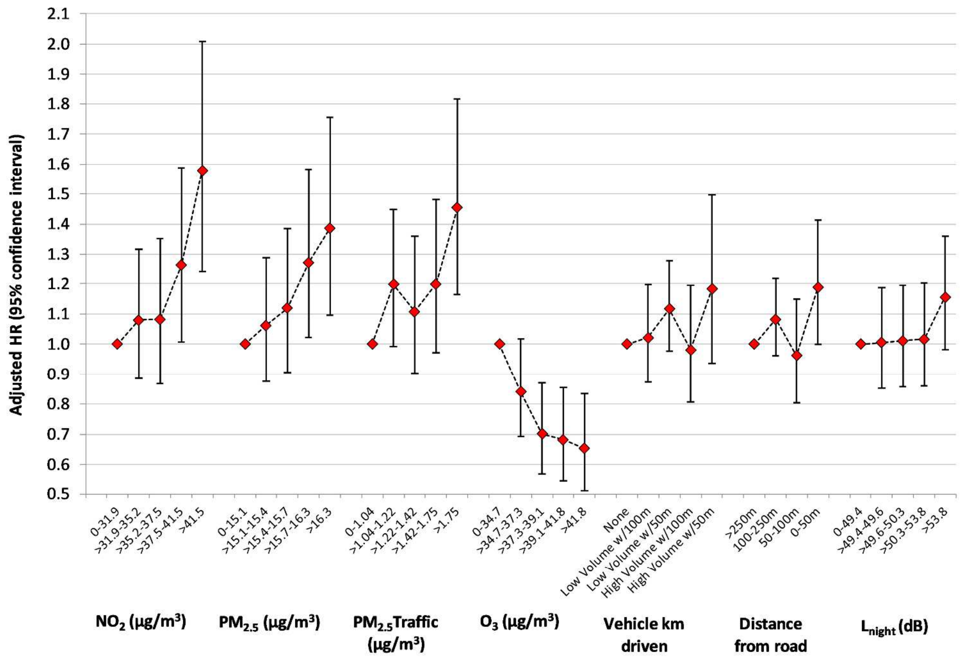

Figure 1 – Adjusted hazard ratios (HRs) for all incident dementia during 2005-2011 by air and noise pollution fifths and traffic distance and intensity categories. HRs estimated from cox model with practice fitted as shared-frailty. Adjusted for age, gender, ethnicity, smoking, alcohol consumption, BMI, IMD and co-morbidity (IHD, Stroke, Diabetes, Heart Failure, COPD).

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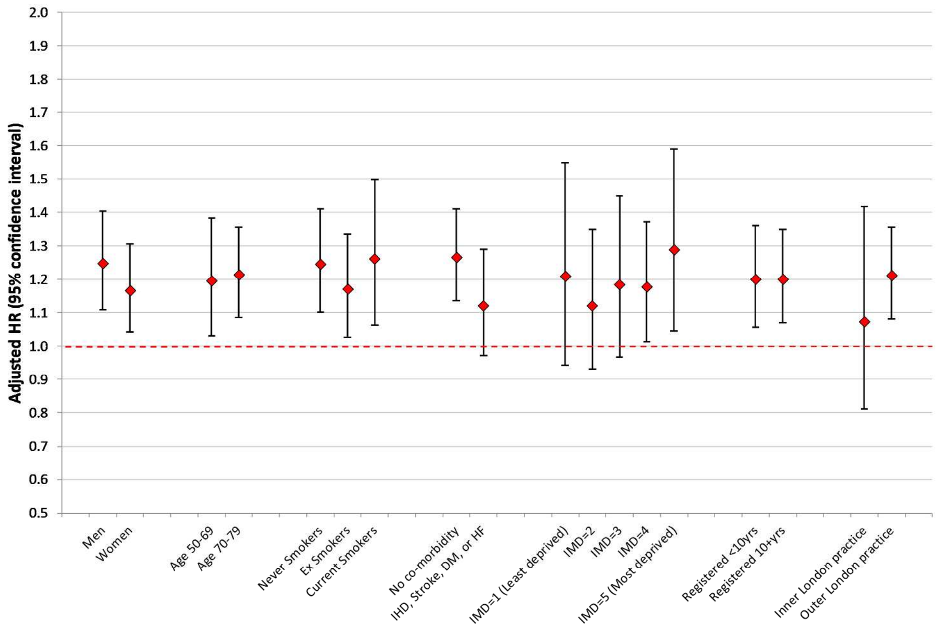

Figure 2 – Stratified adjusted hazard ratios (HRs) for an inter-quartile increase (7.5 µg/m3) in NO2 and all incident dementia during 2005-2011. HRs estimated from cox model with practice fitted as shared-frailty. Adjusted for age, gender, ethnicity, smoking, alcohol consumption and BMI.

278x188mm (300 x 300 DPI)

Supplementary Data

Table S1 – Hazard ratios for dementia during 2005-2011 for an inter-quartile change in NO_2, by different approaches of accounting for practice clustering

Exposure	**Change**	**HR** (95% CI)	**HR** (95% CI)	**HR3**[c] (95% CI)
		Stratified by practice	Practice fitted as fixed effect	Mean practice exposure level fitted
NO_2 (Individual level)	+7.47 μg/m^3	1.21 (1.02-1.44)	1.21 (0.96-1.53)	1.20 (0.96-1.51)
NO_2 (Practice mean level*)	+7.47 μg/m^3	–	–	1.02 (0.77-1.35)

All models adjust for age, gender, ethnicity, smoking, alcohol consumption & BMI. In the non-stratified models, robust standard errors accounting for the clustering by practice are also fitted.
* - Practice mean level is fitted alongside individual level to directly obtain within and between practice estimates (see Begg et al. Separation of individual-level and cluster-level covariate effects in regression analysis of correlated data. *StatMed.* 2003;22(16):2591-602).

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3
		(*b*) Report category boundaries when continuous variables were categorized	Table 4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 4, Figures 1,2
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18, Reference 16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Are noise and air pollution related to the incidence of dementia? A cohort study in London, England

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Are noise and air pollution related to the incidence of dementia? A cohort study in London, England

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Word Count = 4,416

Abstract

Objectives

To investigate whether the incidence of dementia is related to residential levels of air and noise pollution in London.

Design

Retrospective cohort study using primary care data.

Setting

75 Greater London practices.

Participants

130,978 adults aged 50-79 years registered with their general practices on 1/1/2005, with no history of dementia or care home residence.

Primary and Secondary Outcome Measures

A first recorded diagnosis of dementia, and where specified, sub-groups of Alzheimer's and vascular dementia during 2005-13. Average annual concentrations during 2004 for nitrogen dioxide (NO_2), particulate matter with a median aerodynamic diameter ≤2.5μm ($PM_{2.5}$) and ozone (O_3) were estimated at 20m x 20m resolution from dispersion models. Traffic intensity, distance from major road and night-time noise levels (L_{night}) were estimated at postcode level. All exposure measures were linked anonymously to clinical data via residential postcode. Hazard ratios (HRs) from Cox models were adjusted for age, sex, ethnicity, smoking & BMI, with further adjustment explored for area deprivation and co-morbidity.

Results

2,181 subjects (1.7%) received an incident diagnosis of dementia (39% mentioning Alzheimer's disease, 29% vascular dementia). There was a positive exposure response relationship between dementia and all measures of air pollution except O_3, which was not readily explained by further adjustment. Adults living in areas with the highest fifth of NO_2 concentration (>41.5 μg/m^3) versus the lowest fifth (<31.9 μg/m^3) were at higher risk of dementia (HR=1.58, 95% CI 1.24-2.01). Increases in dementia risk were also observed with $PM_{2.5}$, $PM_{2.5}$ specifically from primary traffic sources only, and L_{night}, but only NO_2 and $PM_{2.5}$ remained statistically significant in multi-pollutant models. Associations were more consistent for Alzheimer's disease than vascular dementia.

Conclusions

We have found evidence of a positive association between residential levels of air pollution across London and being diagnosed with dementia, which is unexplained by known confounding factors.

Word Count = 299 words

Strengths and Limitations of this study (5 Max)

- Annual concentrations during 2004 forair and noise pollution exposure were modelled at a fine resolution including near road estimates of traffic pollution
- Anonymous linkage of pollution data to electronic health records of over 100,000 older adults registered with 75 general practices in Greater London during 2005-2013
- Incident dementia diagnoses were identified including Alzheimer's disease and vascular dementia
- Robustness of results was tested for by adjusting for area deprivation and other co-morbidities
- Accuracy and completeness of primary care diagnoses of dementia and sub-diagnoses is a known issue

Background

Dementia, encompassing both vascular dementia and Alzheimer's disease, is now reported as the leading cause of death in England and Wales accounting for 12% of all registered deaths.[1] While temporal changes in recording may have influenced how underlying cause is now determined, more important are increases in longevity among the population at older ages, caused by declining trends in deaths from cardiovascular and cerebrovascular disease.[2] In terms of years of life lost, the Global Burden of Disease in 2013 ranked all dementia as the fifth leading cause,[2] noting their increasing importance as a cause of death despite little change in age-standardised rates. Therefore, primary prevention of all dementia is a major global public health concern for the coming decades.[3] For Alzheimer's disease for example, while it has been estimated that small delays in its onset and progression could significantly reduce its estimated future burden,[4] research has primarily focussed on lifestyle factors where a large systematic review estimated that about a third of Alzheimer's disease may be attributable to potentially modifiable risk factors such as smoking and physical inactivity.[5]

More recently research has also extended to the role of environmental risk factors and dementia, where a large systematic review identified moderate evidence for an association with 8 different factors including air pollution.[6] While air pollution is a well-established risk factor for cardiovascular and respiratory disease,[7] its role in relation to dementia is less well considered and understood.[8] A recent systematic review of the epidemiologic evidence linking air pollution to dementia related outcomes, identified 18 studies, with most reporting adverse associations.[9] However, there was significant variation in the size and quality of the studies involved, re-iterating the noted lack of robust longitudinal or population based studies[6,8]. Subsequently, a large population-based study in Ontario, Canada reported that living close to major roads was associated with a higher incidence of dementia,[10] with a further analysis revealing corresponding associations with modelled levels of nitrogen dioxide (NO_2) and mass of fine particulate matter with a median aerodynamic diameter ≤2.5μm ($PM_{2.5}$).[11] These findings not only raise questions around the mechanisms for the early development of neuroinflammation and neurodegeneration,[12] but require further exploration and replication in other large population cohorts with different exposure models, including traffic noise which has been linked to cognitive decline in adults.[13]

In this paper, we use modelled estimates at a fine spatial scale for modelled estimates of air and noise pollution to investigate relationships with the incidence of dementia across Greater London.

Methods

Data Source

The Clinical Practice Research Datalink (CPRD) is a large, validated primary care database that has been collecting anonymous patient data from participating UK general practices since 1987.[14] It has been shown to be broadly representative of the UK population, with about 7% of all people in the UK actively registered on it in 2011. [14] Approximately three-quarters of contributing CPRD practices in England have consented to their data being linked to external sources. This is facilitated by a “trusted third party” to CPRD, ensuring that researchers have no access to geographical identifiers such as residential postcode. Key variables which have been linked to the practice data include the Index of Multiple Deprivation (IMD), a composite small-area (approximately 1500 people) measure used in England for allocation of resources,[15] and Office for National Statistics (ONS) death registration data, which allows underlying cause of death to be identified. For this study, we selected 75 (linked) practices that lay within the study area bounded geographically by the orbital M25 motorway around Greater London (60 were in outer London boroughs, 15 were in inner London boroughs) that were continually recording data between 2004-2010.[16]

Estimates of Air and Noise Pollution Exposure

The following measures of exposure, estimated annually between 2004 and 2010, were linked to CPRD: (i) air pollution concentrations, (ii) traffic intensity or distance measures, (iii) road traffic noise levels. A priori we chose to focus on annual concentrations estimated in 2004 as this was the earliest year linked. Modelled estimates in other years (2005-2010) were highly correlated (r>0.99), and repeating the analysis using alternative years produced identical results (data not shown).

Modelled annual concentrations for air pollutants were estimated using the KCLurban dispersion modelling system at a resolution of 20m x 20m.[17] It incorporates hourly meteorological measurements, empirically derived concentrations of NO-NO_2-O_3 and derived PM (particulate matter), using information on source emissions from the London Atmospheric Emissions Inventory.[18] For this analysis, we focused on annual concentrations in 2004 for NO_2 (nitrogen dioxide), $PM_{2.5}$ (fine particulate matter with a median aerodynamic diameter ≤2.5μm) and O_3 (ozone). Additionally, we present an estimate for primary $PM_{2.5}$ attributable to road traffic sources estimated from the sum of contributions from the following emissions sources: tyre, brake, exhaust, surface wear and resuspension.[17] Air pollution concentration estimates were derived for each of the 190,115 London postcodes address centroids based on interpolation from the closest 20x20m point of the dispersion model.[18] This resulted in patients residing in the same postcodes, which typically average about 15 households nationally, being assigned the same exposure levels. Additionally, some postcodes covering smaller geographical areas may also be assigned to the same 20x20m point. The exposure concentrations were linked to CPRD by the“trusted third party”, who subsequently remove the postcode, ensuring we had no direct access to any geographical identifiers.

Traffic proximity measures were developed relating to ‘heavy’ vehicle density, which was defined as: light goods vehicles, heavy goods vehicles (rigid and articulated trucks/lorries), buses and coaches. We included a distance measure (in metres) from the postcode centroid to the nearest road classified in the top quartile of heavy vehicle intensity. Traffic intensity was estimated as total vehicle km driven (heavy vehicles only) in each year for all major roads that fell within a 50m and 50-100m radius of the postcode address centroid. We used an arbitrary cut-off >100,000km driven to define ‘high volume’ in the analyses.

Road traffic noise levels were estimated using the TRAffic Noise EXposure (TRANEX) model[19]. This uses information on road traffic flows and speeds, road geography, land cover, and building heights to estimate average sound pressure level (LA_{eq}) in decibels (dB) over different time periods. Evaluations of TRANEX in two other English cities have shown high correlation (r≥0.85) between modelled and measured one-hour LA_{eq}[19]. In our analysis, we focused on average annual L_{night} recorded overnight between 23:00-07:00, as this period represents when most of our study subjects would be at their residence. Alternative analyses using daytime noise (L_{Aeq16}) produced identical results (data not shown) due to the extremely high correlation with night noise (r=0.999).[20] For the linkage of the noise model to CPRD, the geometric centroids of the address locations in each postcode were directly used.

Cohort Definition

Among the 75 practices, a total of 555,385 patients were actively registered on 1/1/2005, representing about 7% of the Greater London population at that time. From these, we selected 139,718 adults aged 50-79 years who had been registered for ≥1 year continuously with their practice. From this group, 131,869 (94%) were successfully linked to our pollution exposures. Non-linkage was mainly due to a few practices being near the study area boundary, so many of their patients' individual postcodes were not eligible. Patients were followed until the earliest of: (i) date of first diagnosis of dementia, (ii) date of death or de-registration from practice, (iii) date when practice ceased contributing to CPRD, (iv) 31/12/2013.

We searched the primary care records for the date of first dementia diagnosis, using the Read codes for dementia within the Quality and Outcomes Framework (QOF).[21] Although most Read codes are non-specific, we identified sub-groups that classified the dementia as Alzheimer's disease or vascular dementia. Using the death records, we also used ICD-10 codes to identify patients with dementia listed as primary cause of death (if not coded as such on the GP record), and to further classify them based on specific mention of Alzheimer's disease or vascular dementia anywhere on the death record. We also extracted from the GP record information on ethnicity, smoking, BMI and alcohol consumption, using the last measurement before baseline when available, or during the study if that was the only one available. A missing category was retained where no information was available. In addition, we extracted information on co-morbidity recorded at baseline, based on a list of conditions we have previously shown to be independently predictive of mortality.[22]

Patients (n=391) with an existing diagnosis for dementia by 1/1/2005 were excluded. Additionally, we sought to exclude patients (n=423) where there was evidence on their medical record that they were living in a residential or care home as of 1/1/2005. We did this through a combination of Read codes, or where 4 or more patients aged 65-99 were recorded living at the same address. We also excluded a small number of patients (n=77) where no IMD could be assigned. This resulted in 130,978 eligible patients for our analyses.

Statistical Analyses

We used Cox proportional hazards models to investigate associations between all exposure measures estimated in the year before baseline (2004) and subsequent dementia incidence. To account for the clustering by practice (homogeneity between patients from the same practice), we fitted models with a shared frailty (at practice level), which are the survival data equivalent to random effects.[23] We adjusted cumulatively for: (1) age, sex, ethnicity, smoking and BMI (recorded alcohol consumption was not independently predictive and dropped from the model), (2) IMD Decile (based on national ranking across England), (3) co-morbidities (Ischaemic Heart Disease (IHD), stroke, heart failure, diabetes) that were independently predictive of dementia. For model (2) we explored the effect of adjusting for other pollutants (air pollution for noise and vice versa). In sensitivity analyses, we explored within- and between- practice effects by fitting different models (a non-frailty model stratified on practice, practice fitted as a fixed effect, fitting practice mean exposure level in addition to individual level). For all pollutants, we fitted a continuous measure based on an inter-quartile range to enable comparison between estimates, and quintiles to describe the shape of the association. All analyses were carried out in Stata version 13 (StataCorp LP, College Station, TX, USA).

Patient and public involvement

No patients were involved in developing the research question, outcome measures, and overall design of the study. Due to patient anonymity, we are unable to disseminate the results of the research directly to study participants.

Results

During the study follow-up period (mean=6.9 years), a total of 2,181 patients (1.7%, incidence rate 2.4 per 1,000 per year) received a first diagnosis of dementia during follow-up (Table 1). Among those patients diagnosed, 848 (38.9%) had a mention of Alzheimer's disease, 634 (29.1%) mentioned vascular dementia, while 747 (34.3%) received a non-specific Read code. A total of 48 patients (2.2%) received diagnoses for both Alzheimer's disease and vascular dementia. While crude incidence rates for dementia were lowest in smokers, later adjustment for age and other covariates explained this association, however the lowest dementia risk seen in obese subjects persisted (data not shown).

Table 1 – Incidence rates of dementia during follow-up by characteristics of eligible subjects estimated at baseline

Baseline Variable	Grouping	All Subjects		First Diagnosis of Dementia 2005-2013†							
				Any		Alzheimer's		Vascular		Non-specific	
		n	%	n	IR*	n	IR*	n	IR*	n	IR*
	All	130,978	100	2,181	2.40	848	0.93	634	0.69	747	0.82
Sex	Men	65,130	49.7	948	2.14	326	0.73	301	0.68	344	0.78
	Women	65,848	50.3	1,233	2.63	522	1.11	333	0.71	403	0.86
Age	50-59	59,587	45.5	99	0.23	38	0.09	17	0.04	45	0.11
	60-69	41,013	31.3	427	1.49	175	0.61	102	0.36	155	0.54
	70-79	30,378	23.2	1,655	8.27	635	3.14	515	2.54	547	2.70
Ethnicity	White	86,896	66.3	1,791	2.84	703	1.11	524	0.83	607	0.96
	Asian	7,309	5.6	98	1.77	35	0.63	39	0.70	27	0.49
	Black	4,287	3.3	101	3.29	32	1.04	32	1.04	37	1.20
	Unknown	32,486	24.8	191	0.98	78	0.40	39	0.20	76	0.39
Smoking	Never	63,478	48.5	1,108	2.42	473	1.03	293	0.64	362	0.79
	Ex	33,063	25.2	715	3.10	264	1.14	235	1.01	235	1.01
	Current	25,733	19.7	308	1.76	95	0.54	89	0.51	133	0.76
	Missing	8,704	6.7	50	1.09	16	0.35	17	0.37	17	0.37
BMI	<20	5,188	4.0	173	5.09	66	1.93	52	1.52	58	1.69
	20-25	35,642	27.2	702	2.81	276	1.10	201	0.80	237	0.94
	25-30	41,281	31.5	721	2.44	304	1.02	202	0.68	238	0.80
	30+	25,783	19.7	364	1.97	116	0.63	129	0.70	125	0.68
	Missing	23,084	17.6	221	1.51	86	0.59	50	0.34	89	0.61
IHD	Yes	9,928	7.6	342	5.21	91	1.38	141	2.14	117	1.77
	No	121,050	92.4	1,839	2.18	757	0.89	493	0.58	630	0.74
Stroke	Yes	3,647	2.8	190	8.38	40	1.74	99	4.33	57	2.49
	No	127,331	97.2	1,991	2.24	808	0.91	535	0.60	690	0.77
Diabetes	Yes	10,160	7.8	300	4.34	85	1.22	114	1.64	109	1.57
	No	120,818	92.2	1,881	2.24	763	0.90	520	0.62	638	0.76
Heart Failure	Yes	1,704	1.3	62	6.76	9	0.97	26	2.81	27	2.92
	No	129.274	98.7	2,119	2.35	839	0.93	608	0.67	720	0.80
Index of Multiple Deprivation‡	1 (Least)	26,149	20.0	426	2.21	163	0.84	132	0.68	144	0.75
	2	31,452	24.0	535	2.36	212	0.93	146	0.64	188	0.83
	3	26,093	19.9	401	2.29	179	1.02	112	0.64	119	0.68
	4	30,817	23.5	514	2.49	187	0.90	160	0.77	176	0.85
	5 (Most)	16,467	12.6	305	2.78	107	0.97	84	0.76	120	1.09
Borough	Inner	23,111	17.6	390	2.51	123	0.79	134	0.86	143	0.92
	Outer	107,867	82.4	1,791	2.37	725	0.96	500	0.66	604	0.80
Registration Length	<10 years	40,386	30.8	638	2.41	251	0.94	196	0.74	210	0.79
	10+ years	90,592	69.2	1,543	2.39	597	0.92	438	0.68	537	0.83

* - Incidence Rate per 1,000 patients per year, † - N=48 patients appear in both Alzheimer's and vascular dementia category, ‡ - These groups correspond to fifths of IMD ranking across England, thus Greater London is under represented in the most deprived fifth.

Summary statistics for the modelled air and noise pollutants in 2004 are shown in Table 2. All air pollutants were strongly positively related to each other (r>0.9), except for O_3 which was negatively correlated (r=-0.9 or greater) with both NO_2 and $PM_{2.5}$. Night noise (L_{night}) was positively related to NO_2 and $PM_{2.5}$, but associations were less in magnitude (r=0.3 to 0.4) to all air pollutants. A different pattern for noise was also observed when intra-class correlations (ICC) were calculated by practice. While most variation by noise was observed within practices (ICC=0.05), the opposite was true for air pollutants where most variation was between practice (ICCs>0.7). When mean concentrations were calculated by traffic distance and intensity (Supplemental Table S1), all pollutants declined with increasing distance from major roads, except O_3 which was higher with further distance. While patients residing in postcodes closest to major roads (0-50m) had much higher night noise levels than those furthest away (60.4 vs. 50.9dB), the difference in modelled air pollution concentrations, especially $PM_{2.5}$, was much less.

Table 2 – Summary statistics for the annual concentrations in 2004 of air (NO_2, $PM_{2.5}$, $PM_{2.5}$ Traffic, O_3) and noise (L_{night}) pollutants

Summary Statistic		NO_2 (μg/m^3)	$PM_{2.5}$ (μg/m^3)	$PM_{2.5}$ (Traffic) (μg/m^3)	O_3 (μg/m^3)	L_{night} (dB)
Mean ±SD		37.1 ±5.7	15.7 ±0.8	1.4 ±0.5	38.0 ±3.9	52.1 ±4.6
Median (IQR*)		36.4 (32.9-40.4)	15.6 (15.2-16.1)	1.3 (1.1-1.7)	38.2 (35.5-41.0)	49.9 (49.4-52.1)
Correlation coefficients	NO_2	_	0.98	0.94	-0.99	0.33
	$PM_{2.5}$	0.98	_	0.97	-0.96	0.39
	$PM_{2.5}$ (Traffic)	0.94	0.97	_	-0.90	0.51
	O_3	-0.99	-0.96	-0.90	_	-0.27
	L_{night}	0.33	0.39	0.51	-0.27	_
	ICC (Practice)	0.87	0.83	0.68	0.92	0.05

* - Inter-quartile range, † - Intra-class coefficient calculated across practice clusters

Table 3 summarises a series of adjusted hazard ratios for an incident diagnosis of dementia associated with comparable inter-quartile changes in different pollutant exposures. The strongest positive associations were seen for NO_2 where a +7.5 μg/m^3 change produced a HR=1.16 (95% CI 1.05-1.28), adjusting for IMD and other confounders (HR2 in Table 3). Further adjustment for related co-morbidities (HR3=1.16) did not explain this association. Corresponding associations were smaller with other measures ($PM_{2.5}$ HR=1.07, $PM_{2.5}$ Traffic HR=1.08, L_{night} HR=1.02, Distance from road HR=1.02) or negative (O_3 HR=0.84). We explored different approaches in estimating within- and between- practice estimates (Supplemental Table S2). For NO_2 and $PM_{2.5}$ HRs were >1 for both estimates, but confidence intervals were wide. For night noise (L_{night}), there was stronger evidence suggestion of a between-practice association (HR=1.42, 95% CI 1.03-1.96).

To investigate the shape of the association, Figure 1 plots the adjusted hazard ratio (HR3 in Table 3) by air and noise pollution fifths, and road distance and traffic intensity 50m categories. The corresponding HRs are given in full in Supplementary Table S3. For NO_2 and $PM_{2.5}$ the increase in dementia risk was noticeably higher in the top fifth of exposure. Patients with an assigned annual exposure of NO_2 of >41.5 μg/m^3 had a marked increase in risk (HR=1.40, 95% CI 1.12-1.74) compared to those in the bottom fifth (<31.9 μg/m^3). For other measures (noise, distance, intensity), there was less evidence of any trend, while for O_3 the risk was highest in the lowest fifth of exposure (<34.7 μg/m^3).

The associations between dementia and an interquartile change (+7.5 μg/m^3) in NO_2 are explored further in Figure 2, which plots adjusted hazard ratios (HR2 in Table 3) from Cox models stratified on a series of risk factors. Generally, there was little evidence of any effect modification across these factors, with all categories producing a HR>1. Associations between NO_2 and dementia were still observed when restricted to patients registered for their practice continually for more than 10 years (HR=1.13, 95%CI 1.01-1.26), or to patients without IHD, stroke, diabetes or heart failure at baseline (HR=1.21, 95%CI 1.08-1.34).

Table 3 – Adjusted hazard ratios for incident Dementia during 2005-2013 by traffic related exposures

Exposure	**IQR Change**	**HR1**[a] (95% CI)	**HR2**[b] (95% CI)	**HR3**[c] (95% CI)	**HR4**[d] (95% CI)
NO_2	+7.47 $\mu g/m^3$	1.17 (1.06-1.28)	1.16 (1.05-1.28)	1.16 (1.05-1.27)	1.15 (1.04-1.28)
$PM_{2.5}$	+0.95 $\mu g/m^3$	1.07 (1.02-1.12)	1.07 (1.02-1.12)	1.06 (1.02-1.12)	1.06 (1.01-1.13)
$PM_{2.5}$ (Traffic)	+0.58 $\mu g/m^3$	1.09 (1.02-1.17)	1.08 (1.01-1.16)	1.08 (1.01-1.16)	1.08 (0.99-1.18)
O_3	+5.56 $\mu g/m^3$	0.84 (0.75-0.93)	0.84 (0.75-0.94)	0.85 (0.76-0.94)	0.85 (0.76-0.96)
L_{night}	+ 2.68 dB	1.02 (1.00-1.05)	1.02 (1.00-1.05)	1.02 (1.00-1.05)	1.01 (0.98-1.03)
Distance to major road	- 310 m	1.02 (0.97-1.08)	1.02 (0.97-1.08)	1.02 (0.97-1.08)	1.00 (0.95-1.05)

[a] HR1: Cox model with practice fitted as shared-frailty. Adjusted for age, sex ethnicity, smoking & BMI.
[b] HR2: As HR1, plus additional adjustment for IMD.
[c] HR3: As HR2, plus additional adjustment for co-morbidity (IHD, Stroke, Diabetes, Heart Failure).
[d] HR4: As HR2, plus additional adjustment for L_{night} (NO_2 and $PM_{2.5}$ estimates) or NO_2 (L_{night} and Distance estimates).

We repeated the analysis, now sub-classifying dementia diagnoses recorded as Alzheimer's disease, vascular dementia, or non-specific where no further information was available (Table 4). The positive associations with NO_2 and $PM_{2.5}$ were more consistent for Alzheimer's disease and non-specific diagnoses. For example, patients in the top fifth exposure category of NO_2 (>41.5 µg/m^3) were at higher risk of receiving an Alzheimer's diagnosis than patients in bottom fifth (HR=1.50, 95% CI 1.08-2.08). For vascular dementia, there was less evidence of a consistent effects with air or noise pollution.

Table 4 – Hazard ratios for incident Alzheimer's disease and vascular dementia during 2005-2013 by air and noise pollutants

		Alzheimer's Disease	Vascular Dementia	Non-specific
Exposure	**Category / IQR Change**	**HR2**[a] (95% CI)	**HR2**[a] (95% CI)	**HR2**[a] (95% CI)
NO_2	0-31.9	1 (Reference)	1 (Reference)	1 (Reference)
	>31.9-35.2	0.98 (0.74-1.28)	0.94 (0.69-1.29)	1.09 (0.84-1.40)
	>35.2-37.5	0.99 (0.73-1.35)	0.83 (0.57-1.20)	1.08 (0.82-1.43)
	>37.5-41.5	1.15 (0.84-1.58)	0.98 (0.66-1.44)	1.01 (0.75-1.35)
	>41.5	1.50 (1.08-2.08)	1.01 (0.66-1.55)	1.55 (1.16-2.07)
	+7.5 $\mu g/m^3$	1.23 (1.07-1.43)	1.15 (0.96-1.39)	1.13 (0.99-1.28)
$PM_{2.5}$	0-15.1	1 (Reference)	1 (Reference)	1 (Reference)
	>15.1-15.4	1.01 (0.77-1.32)	0.89 (0.66-1.20)	1.00 (0.77-1.28)
	>15.4-15.7	1.13 (0.84-1.52)	0.72 (0.50-1.02)	1.13 (0.86-1.47)
	>15.7-16.3	1.24 (0.92-1.68)	0.91 (0.63-1.32)	1.00 (0.76-1.33)
	>16.3	1.42 (1.03-1.96)	0.86 (0.57-1.30)	1.33 (0.99-1.77)
	+0.9 $\mu g/m^3$	1.10 (1.02-1.18)	1.06 (0.97-1.16)	1.06 (0.99-1.13)
$PM_{2.5}$ Traffic	0-1.04	1 (Reference)	1 (Reference)	1 (Reference)
	>1.04-1.22	1.00 (0.76-1.30)	1.14 (0.86-1.52)	1.07 (0.84-1.38)
	>1.22-1.42	1.09 (0.82-1.45)	0.92 (0.66-1.27)	1.06 (0.81-1.38)
	>1.42-1.75	1.23 (0.93-1.64)	0.90 (0.63-1.28)	0.97 (0.73-1.27)
	>1.75	1.46 (1.08-1.98)	0.99 (0.68-1.44)	1.33 (1.00-1.75)
	+0.58 $\mu g/m^3$	1.13 (1.02-1.26)	1.08 (0.95-1.23)	1.08 (0.97-1.19)
0_3	0-34.7	1 (Reference)	1 (Reference)	1 (Reference)
	>34.7-37.3	0.83 (0.65-1.07)	0.88 (0.63-1.24)	0.68 (0.52-0.89)
	>37.3-39.1	0.64 (0.48-0.86)	0.81 (0.55-1.17)	0.76 (0.58-1.00)
	>39.1-41.8	0.62 (0.46-0.85)	0.82 (0.55-1.23)	0.73 (0.55-0.96)
	>41.8	0.67 (0.48-0.94)	0.92 (0.59-1.43)	0.67 (0.50-0.90)
	+5.6 $\mu g/m^3$	0.78 (0.66-0.92)	0.88 (0.71-1.09)	0.87 (0.76-1.01)
L_{night}	0-49.4	1 (Reference)	1 (Reference)	1 (Reference)
	>49.4-49.6	0.95 (0.76-1.18)	1.22 (0.94-1.58)	1.07 (0.85-1.34)
	>49.6-50.3	0.96 (0.77-1.20)	1.23 (0.94-1.59)	0.97 (0.77-1.23)
	>50.3-53.8	0.94 (0.75-1.18)	1.17 (0.90-1.52)	0.93 (0.73-1.19)
	>53.8	1.05 (0.84-1.31)	1.09 (0.83-1.42)	1.14 (0.91-1.43)
	+ 2.7 dB	1.03 (0.99-1.07)	1.00 (0.96-1.05)	1.03 (0.99-1.07)

[a] HR2: Cox model with practice fitted as shared-frailty. Adjusted for age, sex, ethnicity, smoking, alcohol consumption, BMI & IMD.

Discussion

In a sample of 75 general practices across Greater London the recording of new dementia diagnoses was positively associated with measures of NO_2 and $PM_{2.5}$ assigned at residential address at beginning of the incident period. The association could not be explained by confounding, and was consistent within sub-groups. When we restricted to specific diagnoses, associations were still observed with Alzheimer's disease but not vascular dementia.

Strengths and Weaknesses

While we were able to link pollution exposures to the primary care record to obtain diagnoses of dementia, there are concerns around the variability of dementia diagnoses in UK primary care,[24] and a recent review has concluded that dementia diagnoses on primary care databases may not be an accurate reflection of the true prevalence.[25] Under-recording is thought to be a common issue, as the diagnosis is associated with a stigma for many, and GP's may be reluctant to diagnose dementia unless highly certain.[26] A recent study across 23 London practices increased the prevalence on their QOF dementia registers by 9% by a simple coding review.[26] To account for under-recording at baseline, a priori we decided to exclude all patients identified as living in care homes at the beginning of follow-up regardless of dementia diagnosis. During follow-up, we observed broadly similar number of dementia sub-types being newly diagnosed, and since it is expected that about two-thirds of dementia is Alzheimer's disease,[27] this suggests the under-recording of Alzheimer's disease in particular may be an issue. Under-recording in our study could be problematic if it was related to key practice characteristics such as deprivation, as dementia recording has been shown to be lower among more affluent practices.[24,28] In our study we observed a wide range of incident rates by practice (0.2% to 8.4%), and since the majority of air pollution variation was between practices, we cannot discount unmeasured practice characteristics as a possible explanation for our findings. There are also known variations in the prevalence and diagnosis rates of dementia across England,[24] with London being among the reported lowest[29], so we also have to acknowledge that the associations we observed may be specific within London and may not extend nationally.

Another weakness of the study is the lack of historical data surrounding exposure. Most large epidemiological studies of long-term exposure to pollution will have difficulty capturing an accurate picture of lifetime or cumulative exposure. This may be pertinent for Alzheimer's disease where the pathogenesis of the disease may take place over many years.[30] We did not have any information relating to previous address or location, and the London population is thought to be mobile and dynamic over time.[31] Thus, we are making an assumption that an annual estimate for a single year (2004) represents long-term exposure, based on the last known address for the patient at that practice. We tested this in two ways: (i) sensitivity analyses based on patients who had been continually registered at their practice for a long time (>10years) produced similar findings, (ii) where we did have other modelled years available during follow-up (2005-2010), these were highly correlated over time (r>0.95), so alternative analyses using them made no discernible difference. However, we cannot discount historical factors as an explanation for our findings. For example, it could be that recent exposure levels are acting as a proxy for other historical environmental factors linked to pollution, such as lead from petrol,[32] where cumulative exposure has been linked to cognitive decline in later life.[33]

A novel aspect of our analysis was the ability to simultaneously study the modelled effects of air and noise pollution on dementia, overcoming acknowledged limitations from other studies.[11,34] Previous validation of the pollution models used in this study had shown low roadside correlation between them, suggesting that the independent effects of traffic pollution and road noise can be investigated.[20] However, a potential limitation is that by being based within Greater London, our air pollution exposure estimates may be somewhat homogeneous, lacking the variability we would expect to see nationally when more rural geographical areas are included. Within London, the contribution of regional (background) $PM_{2.5}$ and O_3 to overall levels tends to dominate.[17] However, we were able to make use of a dispersion model with exceptionally fine resolution (20m x 20m), to estimate significant changes in exposure of air pollution such as NO_2, between major roads and suburban background locations.[17] Despite this, the reality was that subtle roadside changes predicted by the model were small in comparison to larger differences estimated between the areas represented by the GP practices (ICCs>0.7 for all air pollutants), suggesting most modelled air pollution variation was between (practice) areas.[16] While this limited statistical power to test for any within practice effects in the study, we did not find evidence to suggest that the overall associations with NO_2 and $PM_{2.5}$ were entirely explained by between practice differences in modelled exposures.

Finally, another limitation was limited or incomplete information on key confounders, and reliance on an area-based measure (IMD) for socio-economic status. While mid-life obesity is a risk factor for Alzheimer's disease,[5] the BMI measures we extracted around baseline showed that the risk declined with obesity in later life, a finding which has been observed elsewhere.[35] However, further adjustment for IHD, stroke, dementia and heart failure, which would be associated with earlier unmeasured risk factors, including individual socio-economic status, did not explain our findings.

Context

The established body of epidemiological evidence linking long term concentrations of air pollution to adverse health effects has mainly focussed on cardiovascular disease[36]. The Global Burden of Disease studies which have described the worldwide impact of air pollution, considered a wide range of outcomes (ischaemic heart disease, stroke, lung cancer, chronic obstructive pulmonary disease) but did not consider neurodegenerative outcomes.[7] Research linking air pollution exposure to neurocognitive function has gradually increased from observational findings in 2002 from dogs in Mexico City,[37] to larger studies which assessed cognitive decline,[38,39] and large population cohorts that specifically investigated the association in relation to diagnoses of dementia.[10,11,40-43]

A 2015 review on the effect of long-term exposure to outdoor air pollution (15 studies) and noise (8 studies) on cognitive and psychological functions in adults showed that both exposures were separately shown to be associated with one or several measures of global cognitive function, but no study considered both exposures simultaneously, which they highlighted as a need for further research.[34] The same authors followed with data from the Heinz Nixdorf Recall cohort study,[13] on 4,086 adults using an additively calculated global cognitive score. They concluded "air pollution and road traffic noise might act synergistically on cognitive function in adults". Our study could consider both measures (air pollution and night noise), and while both showed independent associations with dementia, in a combined model any associations with noise were diminished and of borderline statistical significance.

The largest cohort studies to date investigating dementia and long-term exposure to air pollution are from North America[10,11,43]. Chen et al[10,11] used a large Canadian population based cohort of over 2 million adults aged 55-85 years to ascertain approximately 250,000 incident dementia cases during 2001-13. In their first analysis,[10] the authors found that the risk of dementia increased with nearness to a major road (adjusted HR=1.07 95%CI 1.06–1.08, for people living <50m from a major traffic road versus >300m). Associations were stronger among urban residents, especially those who lived in major cities. In a subsequent analysis,[11] they used land-use regression models to estimate associations between incident dementia and air pollution, findings significant positive associations with both $PM_{2.5}$ and NO_2,, and smaller negative asscisations with O_3. An interquartile-range increase in $PM_{2.5}$ (4.8μg/m^3) was associated with a HR=1.04 (95%CI 1.03–1.05), while for NO_2 (14.2ppb) it was estimated to be HR=1.10 (95%CI 1.08–1.12). By comparison, our estimated distribution of the same pollutants within Greater London was much less spread, with IQRs almost a fifth smaller. Therefore, comparative HR's for similar unit changes in our study are much greater (e.g. for a 1μg/m^3 change in $PM_{2.5}$ the HR would be 1.07 compared to 1.01 from the Canadian study, for NO_2 this would be 1.02 vs. 1.00). Our estimate for $PM_{2.5}$ was more in line what was found in a large US study of Medicare enrolees for first-ever hospitalisation for dementia during 1999-2010 (HR=1.08, 95% 1.05-1.11 for a 1μg/m^3 change in $PM_{2.5}$). Chen et al speculate that the stronger associations observed with NO_2 may be in part be due to it better capturing fine-scale variability in traffic-related air pollution, whereas $PM_{2.5}$ and O_3 have larger regional components.[11] However the resolution of their air pollution models was coarser (1km x 1km resolution) than in our study (20m x 20m) and may not capture primary emissions from road traffic. While our models were able to estimate traffic-specific components of $PM_{2.5}$,[17] effect estimates remained higher for NO_2.

Some smaller studies have separated Alzheimer's disease from dementia. In Europe, a 15-year longitudinal study in northern Swedish city found evidence of positive associations with both with vascular dementia and Alzheimer's disease and Nitrogen Oxide (NO_x) using a land-use regression model with a spatial resolution of 50m x 50m.[41] Comparison between participants in the highest quartile of residential exposure at baseline, versus those in the lowest, produced similar estimates were similar for Alzheimer's disease (HR=1.38) and vascular dementia (HR=1.47). There have been recent cohort studies from Taiwan: Jung el al[40] showed long-term exposure to O_3 and $PM_{2.5}$ was shown to increase risk of Alzheimer's, while Chang et al[42] found associations between dementia and NO_2 and carbon monoxide. A smaller case-control study by Wu et al[44] linked PM_{10} and O_3 to an increased risk of Alzheimer's and (vascular) dementia. In our study, lower O_3 was negatively associated with risk of dementia, primarily as a result of the strong negative correlation with the other modelled air pollutants.[45]

Implications

The implications of linking exposure to air pollution such as NO_2 to the development of dementia, specifically Alzheimer's disease, raises many questions.[12] The cause of these neurodegenerative diseases is still largely unknown and may be multifactorial.[8] While toxicants from air pollution have several plausible pathways to reach the brain, how and when they may influence neurodegeneration remains speculative.[8,30,46] Traffic related air pollution has been linked to poorer cognitive development in young children,[47] and continued significant exposure may produce neuroinflammation and altered brain innate immune responses in early adulthood.[48] In later life, the risk for accelerated cognitive decline may involve gene-environment interactions, such as that with Apolipoprotein E (APOE),[49] where evidence comes from findings in neurotoxicological experiments with mice.[50]

Our observation of an association of air pollution with new dementia diagnoses among older adults living in Greater London, are in contrast to an earlier analysis on this data which failed to show consistent associations between air pollution and cardiorespiratory outcomes.[16] These suggest there may be a geographical pattern specific to dementia, and potentially Alzheimer's disease, which requires further exploration nationally. In the Ontario cohort, Chen et al estimated that 6.1% of their total dementia cases were attributable to elevated air pollution exposure.[11] In our study, a theoretical shift of all patients to the bottom 20% of NO_2 exposure produces an attributable fraction of 7% (data not shown). While this would be smaller than previous PAF estimates for dementia in the UK for a range of independent risk factors such as for hypertension or obesity,[5] even a small PAF for dementia would be impactful, where environmental risk factors such as air pollution can be more easily modified at population level.[30] There would be significant public health gains even if the impact was only to delay the progression of dementia.[4]

With the future global burden of dementia likely to be substantial,[3] further epidemiological work is urgently needed to confirm and understand better, recent findings linking air pollution to dementia.[8,30] Our results suggest both regional and urban background pollutants may be as important as near-traffic pollutants. Future large-scale studies will need to rely on improved recording and linkage of dementia diagnoses across electronic systems, particularly Alzheimer's disease, where multiple sources can improve diagnostic accuracy.[25] Since exposure is lifelong, and most cases are diagnosed in later life, historical data is also ideally required to better estimate cumulative exposure over preceding decades. In conclusion, our findings add to a growing evidence base linking air pollution and neurodegeneration, and should encourage further research in this area.

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Ethics: This study (protocol number 12_026AR) was approved by the Independent Scientific Advisory Committee evaluation of joint protocols of research involving CPRD data in September 2017.

Contributors: HRA, RWA, JG, SDB, and FJK contributed to the wider study conception and design. HRA, SDB, JG, DD, and FJK contributed to exposure assessment. IMC, RWA and DGC acquired linked health data. IMC conceived the specific study design, conducted the data analyses, and drafted the initial report. HRA, RWA, DGC and DPS all contributed to the data analysis plan. All authors contributed to interpreting the analyses and to critically revising the article and approved the final draft. IMC is the guarantor of the work.

Conflicts of Interest: None

Data Sharing: Due to data restrictions, we are unable to share any aspects of the data.

Figure Titles & Footnotes

Figure 1 – Adjusted hazard ratios (HRs) for all incident dementia during 2005-2013 by air and noise pollution fifths and traffic distance and intensity categories

HRs estimated from cox model with practice fitted as shared-frailty. Adjusted for age, sex, ethnicity, smoking, BMI and IMD. HRs are given in full in Supplementary Table S3.

Figure 2 – Stratified adjusted hazard ratios (HRs) for an inter-quartile increase (7.5 µg/m^3) in NO_2 and all incident dementia during 2005-2013

HRs estimated from cox model with practice fitted as shared-frailty. Adjusted for age, sex, ethnicity, smoking, BMI and IMD. P-values for interaction tests were: age (p=0.75), sex (p=0.27), smoking (p=0.47), co-morbidity (p=0.31), IMD (p=0.72), registration length (p=0.62), practice borough (p=0.63).

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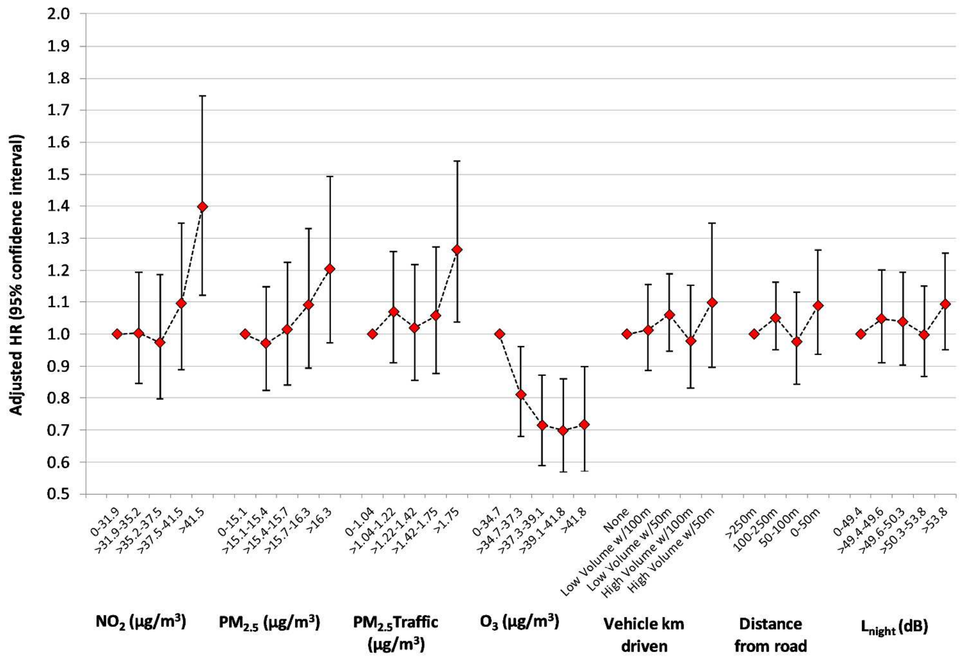

Figure 1 – Adjusted hazard ratios (HRs) for all incident dementia during 2005-2013 by air and noise pollution fifths and traffic distance and intensity categories.

Footnote: HRs estimated from cox model with practice fitted as shared-frailty. Adjusted for age, sex, ethnicity, smoking, BMI and IMD. HRs are given in full in Supplementary Table S3.

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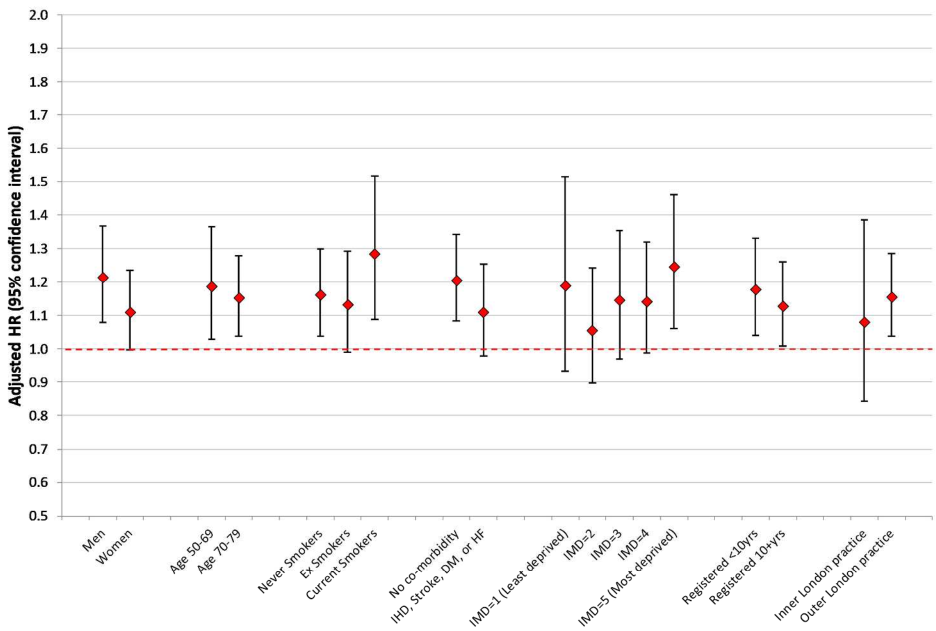

Figure 2 – Stratified adjusted hazard ratios (HRs) for an inter-quartile increase (7.5 µg/m3) in NO2 and all incident dementia during 2005-2013.

Footnote: HRs estimated from cox model with practice fitted as shared-frailty. Adjusted for age, sex, ethnicity, smoking, BMI and IMD. P-values for interaction tests were: age (p=0.75), sex (p=0.27), smoking (p=0.47), co-morbidity (p=0.31), IMD (p=0.72), registration length (p=0.62), practice borough (p=0.63).

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Supplementary Data

Table S1 – Summary of air (NO_2, $PM_{2.5}$, $PM_{2.5}$ Traffic, O_3) and noise (L_{night}) pollutants by traffic volume and major road distance

Traffic exposure	Level	N		NO_2	$PM_{2.5}$	$PM_{2.5}$ (Traffic)	O_3	L_{night}
Vehicle km Driven*	None within 100m	74,913	Mean ±SD	35.8 ±4.6	15.5 ±0.6	1.3 ±0.3	38.8 ±3.4	49.9 ±1.2
	Low within 50-100m	15,995	Mean ±SD	36.5 ±5.0	15.6 ±0.7	1.3 ±0.4	38.3 ±3.7	50.3 ±1.4
	Low within 50m	23,243	Mean ±SD	38.5 ±5.9	15.9 ±0.8	1.6 ±0.5	37.3 ±4.1	57.2 ±4.8
	High within 50-100m	10,400	Mean ±SD	39.6 ±5.9	16.1 ±0.8	1.7 ±0.5	36.3 ±4.1	52.2 ±3.1
	High within 50m	6,427	Mean ±SD	45.6 ±7.3	17.0 ±1.0	2.6 ±0.8	33.2 ±4.3	62.6 ±5.9
Distance(m) to major road†	>250m	59,825	Mean ±SD	35.2 ±4.7	15.4 ±0.7	1.2 ±0.3	39.3 ±3.5	50.9 ±3.3
	100-250m	43,386	Mean ±SD	37.7 ±5.1	15.8 ±0.7	1.4 ±0.4	37.5 ±3.6	51.2 ±3.2
	50-100m	14,708	Mean ±SD	39.4 ±6.0	16.0 ±0.8	1.7 ±0.5	36.5 ±4.1	52.5 ±3.8
	0-50m	12,609	Mean ±SD	41.9 ±7.2	16.5 ±1.0	2.1 ±0.8	35.4 ±4.5	60.4 ±5.7

* >100,000km driven annually by heavy vehicles (see methods) was defined as High Volume, <100,000km defined as Low Volume.
† - Major road defined as top quartile of heavy vehicle intensity

Table S2 – Hazard ratios for dementia during 2005-2011 for an inter-quartile change in NO_2, $PM_{2.5}$ and L_{night} by different approaches of accounting for practice clustering

Exposure	**Change**	**HR** (95% CI)	**HR** (95% CI)	**HR3**[c] (95% CI)
		Stratified by practice	Practice fitted as fixed effect	Mean practice exposure level fitted
NO_2	Individual level change (+7.47 μg/m^3)	1.08 (0.92-1.26)	1.08 (0.88-1.33)	1.07 (0.88-1.32)
	Practice mean level* (+7.47 μg/m^3)	–	–	1.10 (0.84-1.32)
$PM_{2.5}$	Individual level change (+0.95 μg/m^3)	1.03 (0.97-1.10)	1.03 (0.96-1.11)	1.03 (0.96-1.11)
	Practice mean level* (+0.95 μg/m^3)	–	–	1.12 (0.90-1.38)
L_{night}	Individual level change (+2.68 dB)	1.01 (0.99-1.04)	1.01 (0.99-1.04)	1.02 (0.99-1.04)
	Practice mean level* (+2.68 dB)	–	–	1.42 (1.03-1.96)

All models adjust for age, gender, ethnicity, smoking & BMI. In the non-stratified models, robust standard errors accounting for the clustering by practice are also fitted.
* - Practice mean level is fitted alongside individual level to directly obtain within and between practice estimates (see Begg et al. Separation of individual-level and cluster-level covariate effects in regression analysis of correlated data. *StatMed.* 2003;22(16):2591-602).

Table S3 – Hazard ratios from Figure 1

Exposure	Category / IQR Change	HR2[a] (95% CI)
NO_2 ($\mu g/m^3$)	0-31.9	1 (Reference)
	>31.9-35.2	1.01 (0.85-1.19)
	>35.2-37.5	0.97 (0.80-1.19)
	>37.5-41.5	1.10 (0.89-1.35)
	>41.5	1.40 (1.12-1.74)
$PM_{2.5}$ ($\mu g/m^3$)	0-15.1	1 (Reference)
	>15.1-15.4	0.97 (0.82-1.15)
	>15.4-15.7	1.02 (0.84-1.23)
	>15.7-16.3	1.09 (0.90-1.33)
	>16.3	1.20 (0.97-1.49)
$PM_{2.5}$ Traffic ($\mu g/m^3$)	0-1.04	1 (Reference)
	>1.04-1.22	1.07 (0.91-1.26)
	>1.22-1.42	1.02 (0.85-1.22)
	>1.42-1.75	1.06 (0.88-1.27)
	>1.75	1.26 (1.04-1.54)
0_3 ($\mu g/m^3$)	0-34.7	1 (Reference)
	>34.7-37.3	0.81 (0.68-0.96)
	>37.3-39.1	0.72 (0.59-0.87)
	>39.1-41.8	0.70 (0.57-0.86)
	>41.8	0.72 (0.57-0.90)
Vehicle km Driven*	None within 100m	1 (Reference)
	Low within 50-100m	1.01 (0.89-1.15)
	Low within 50m	1.06 (0.95-1.19)
	High within 50-100m	0.98 (0.83-1.15)
	High within 50m	1.10 (0.90-1.35)
Distance(m) to major road†	>250m	1 (Reference)
	100-250m	1.05 (0.95-1.16)
	50-100m	0.98 (0.84-1.13)
	0-50m	1.09 (0.94-1.26)
L_{night} (dB)	0-49.4	1 (Reference)
	>49.4-49.6	1.05 (0.91-1.20)
	>49.6-50.3	1.04 (0.90-1.19)
	>50.3-53.8	1.00 (0.87-1.15)
	>53.8	1.09 (0.95-1.25)

[a] HR2: Cox model with practice fitted as shared-frailty. Adjusted for age, gender, ethnicity, smoking, alcohol consumption, BMI & IMD.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3
		(*b*) Report category boundaries when continuous variables were categorized	Table 4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 4, Figures 1,2
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18, Reference 16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.